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| 09/669,033 | 09/25/2000 | Roderic M K Dale | OLIG-017CON | 5652 |

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| EXAMINER |
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KIM, YOUNG J

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| ART UNIT | PAPER NUMBER |
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1637

DATE MAILED: 10/23/2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n No.

09/669,033

Applicant(s)

DALE, RODERIC M K

Examiner

Young J. Kim

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 August 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18-28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 25-28 is/are allowed.
- 6) ☒ Claim(s) 18-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

This Office Action responds the Amendment received on August 6, 2002 (Paper No. 9).

Preliminary Remarks

The Examiner of record notes that although the Office Action was initially mailed on December 19, 2000, the communication, due to the Office errors, was not mailed to the correct address. The response time, therefore, have been restarted from February 6, 2002, making the Applicant's Amendment received on August 6, 2002 timely.

In the Applicant's response on page 5 under the section "Response to the rejection under 35 U.S.C. 103," Applicant refers to claims 26-29 for correcting the "dependency of the independent claims..." The Examiner of record assumes that this is a typographical error because the Applicant's response added new claims 18-28, and not a claim 29.

Specification

The objection to the specification for containing a misspelled word and failing to comply with the Sequence Rules as set forth in 37 CFR 1.821 to 1.825, in the Office Action mailed on December 19, 2001, is withdrawn in view of the Amendment received on August 6, 2002, amending the specification and complying with the Sequence Rules.

Claim Rejections - 35 USC § 103

The rejection of claims 6-8 under 35 U.S.C. 103(a) as being unpatentable over Graham et al. (US Patent No. 6,127,120, issued October 3, 2000, priority April 21, 1998) in view of Cook et

al. (US Patent No. 6,127,533, issued October 3, 2000, priority February 14, 1997) and Fodor et al. (US Patent No. 5,800,992, issued September 1, 1998, priority March 7, 1990), in the Office Action mailed on December 19, 2001 is withdrawn to the extent that the above recited claims have been cancelled in the Amendment received on August 6, 2002.

The rejection of claims 9-17 under 35 U.S.C. 103(a) as being unpatentable over Graham et al. (US Patent No. 6,127,120, issued October 3, 2000, priority April 21, 1998) in view of Cook et al. (US Patent No. 6,127,533, issued October 3, 2000, priority February 14, 1997), Hacia et al. (US Patent No. 6,013,449, issued January 11, 2000, filed November 26, 1997), McGall et al. (US Patent No. 6,156,501, issued December 5, 2000, priority October 26, 1993), and Fodor et al. (US Patent No. 5,800,992, issued September 1, 1998, priority March 7, 1990), in the Office Action mailed on December 19, 2001 is withdrawn to the extent that the above recited claims have been cancelled in the Amendment received on August 6, 2002.

Rejection – Necessitated by Amendment

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The newly filed base claim 18, differs from the original claim 6 for introducing new limitation of the probes (i.e., acid stability, nuclease resistance), necessitating the instant rejection.

Claims 18-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Graham et al. (US Patent No. 6,127,120, issued October 3, 2000, priority April 21, 1998) in view of Hacia

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et al. (US Patent No. 6,013,449, issued January 11, 2000, filed November 26, 1997), McGall et al. (US Patent No. 6,156,501, issued December 5, 2000, priority October 26, 1993), and Fodor et al. (US Patent No. 5,800,992, issued September 1, 1998, priority March 7, 1990).

Claims are drawn to a method for detecting nucleic acid sequences in two or more collections of nucleic acid molecules wherein a collection of probes are acid/nuclease resistant, and a first set of hybridized nucleic acids are removed via an acidic solution, followed by a subsequent hybridization of a second set of nucleic acids.

Graham et al. disclose a modified polynucleotide probe which "inhibit enzyme degradation while its remaining internucleotide linkages... maintain duplex stability (stable hybridization complex) (column 20, lines 1-5). Graham et al. also disclose that the stage for mounting the sample could be designed to accommodate one or more of the following solid supports, such as silicon wafer, chip, higher density array microwell plate, or a membrane (column 26, lines 19-24). Graham et al. explicitly teach that the modified probes could be plated out on an oligonucleotide array hybridized with mRNA and their hybridization pattern analyzed, followed by treatment with an RNase or alkali for **reuse of the array** (column 31, lines 60-66).

Graham et al. do not disclose the differential labeling of the two nucleic acid molecules.

Graham et al. do not disclose the use of an acidic solution for the removal of hybridized nucleic acids from the arrayed probes for the purpose of reusing the array.

Hacia et al. disclose a two-color labeling nucleic acid hybridization technique (column 13, lines 34-40).

Fodor et al. disclose a method of using a reusable array which allows the hybridization of a set of nucleic acids followed by a removal of the hybridized nucleic acid, and further followed by the hybridization of a second set of nucleic acids. Fodor et al. states that after a particular sequence has been hybridized (i.e., target sequence) and the pattern of the hybridization analyzed, the matrix substrate should be reusable and readily prepared for exposure to a second or subsequent target polynucleotides (column 25, lines 4-8) wherein the array is prepared for reuse by treatment with "various detergents or solvents to which the substrate, the oligonucleotide probes, and the linkages to the substrate are inert... includ[ing] elevated temperature treatment, treatment with organic or inorganic solvents, **modification in pH**, and other means for disrupting specific interactions" (column 25, lines 9-15).

McGall et al. disclose an array of modified oligonucleotide probes, wherein the modification comprise 7-deazaadenine and 7-deazaguanine, in order to stabilize the oligonucleotide probes towards acidic conditions (column 9, lines 47-50) wherein such property could be useful for either the "fabrication or subsequent use (or reuse) of the arrays" (column 9, lines 37-39).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Graham et al., McGall et al., Hacia et al., and Fodor et al. to arrive at the invention as claimed. One of ordinary skill in the art would have been motivated to combine the teachings because by doing so, one of ordinary skill in the art would have been able to reuse the array for multiple hybridization by taking advantage of the modified probes.

In *in re Oetiker*, 977, F.2d 1443, 1448 (Fed. Cir. 1992), the court held that:

"[T]here must be some teaching, reason, suggestion, or motivation found "in the prior art" or "in the prior art references" to make a combination to render an invention obvious

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within the meaning of 35 U.S.C. 103 (1998). Similar language appear in a number of opinions and if taken literally would mean that an invention cannot be held to have been obvious unless something specific in a prior art reference would lead an inventor to combine the teachings therein with another piece of prior art. This restrictive understanding of the concept of obviousness is clearly wrong.... While there must be some teaching, reason, suggestion, or motivation to combine existing elements to produce the claimed device, it is not necessary that the cited references or prior art specifically suggest making the combination.... In sum, it is off the mark for litigants to argue, as many do, that an invention cannot be held to have been obvious unless a suggestion to combine the prior art teachings is found in a specific reference."

Although the cited artisans do not explicitly point out a motivation in their disclosure to combine the teachings of each other, an ordinarily skilled artisan would have been able to identify the need for the combination of the teachings without the disclosure of the instant application. The teachings of Graham et al. and Fodor et al. clearly recognized a need for reusable array of probes (i.e., nuclease resistance and pH stability or probes) and endeavored in such area. McGall et al. also endeavored in the same discipline of reusable arrays wherein the artisans employed acid-resistant probes. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success at combining the teachings of McGall et al. to the teachings of Graham et al. and Fodor et al. to arrive at the claimed method of reusing an array of acid-resistant probes. One of ordinary skill in the art would also have been motivated to combine the differential labeling scheme for hybridization of two different targets, a technique that is well known in the art of hybridization as well as demonstrated by Hacia et al.

It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was

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made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In the Applicant's response, Applicant states that Fodor et al. disclose a matrix substrate which may be reused by treating it with organic or inorganic solvents to which the substrate, the nucleic acid molecules, and their linkages are inert (Response, pp. 5). Applicant also asserts that Fodor et al. disclose that the substrate reuse should employ mild conditions and neutral pH if recycling is desired (Response, pp. 5), concluding that based on these disclosures, Fodor would teach away from the instantly claimed method of employing a wash solution of pH of 0.5-6 for the purpose of reusing the array.

Applicants are advised that Fodor et al. states that, "if a substrate is acid labile," a neutral pH would be preferred in all handling step (column 56, line 5). Fodor et al. was merely expressing that the "modifications in pH" (column 25, line 13), should be designed so as to not "affect the substrate." (column 56, line 4). Contrary to the Applicant's assertion, Fodor et al., in fact, do not teach away from the claimed method, but rather recognizes the need for the artisan to adjust the conditions (i.e., pH) based on the substrate chemistry. Fodor et al. clearly envisioned the use of modifications in pH for reusing the array of probes (column 25, line 13), while recognizing that, "sensitivities...[should] be carefully respected when recycling is desired." (column 56, lines 6-7).

Therefore, the invention as claimed is obvious over the cited references.

Conclusion

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Claims 18-24 are rejected. Claims 25-28 are free of prior art.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Fodor et al. (U.S. Patent No. 5,925,525, issued July 20, 1999, priority June 7, 1989) disclose a method of identifying nucleotide difference via using an array of probes. Although the array of Fodor et al. is disclosed as being reusable, there is neither a suggestion or motivation to use the same array to first hybridize a target nucleic acid, strip the array with an acidic solution, and hybridize subsequently with a reference nucleic acid for the purpose of identifying nucleotide differences. Rather, Fodor et al. identifies nucleotide differences by first hybridizing a target nucleic acid to an array of probes, determine the hybridize pattern, and through a computer, compare the sequence of a reference nucleic acid with the probes that hybridized to the target nucleic acid.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

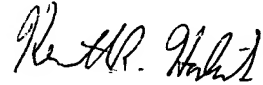
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Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (703) 308-9348. The Examiner can normally be reached from 8:30 a.m. to 7:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (703) 308-1119. Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. The Fax number is (703) 746-3172. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Young J. Kim

10/20/02


KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

10/21/02